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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/438,358	11/12/1999	Gary F. GERARD	0942.4640001	9194

26111 7590 03/10/2004

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/438,358	GERARD ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-51,65-76 and 81-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-51,65-76 and 81-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 12/11/2003, in which several claims were amended (claims 14-15, 19, 31 & 40). Claims 14-51, 65-76, 81-104 are pending and under consideration in the instant application. This action is FINAL.

Response to Arguments

Applicant's arguments filed in the response of 12/11/2003 have been fully considered but they are not persuasive. Before addressing the arguments presented in applicants' latest response, it is noted that applicants would be able to obviate each of the outstanding grounds of rejection by amending the claims to explicitly state that the ribosomal proteins added to the reaction mixture enhance recombinational cloning. Applicants' representative is invited to contact the examiner to work out acceptable language to this effect (e.g. the at least one ribosomal protein is present in an amount sufficient to enhance recombinational cloning).

To the extent that applicants' arguments are a restatement of previous arguments, the examiner's responses previously of record are incorporated here by reference.

Applicants' response essentially argues in each case that the amendment to the claims obviates the outstanding grounds for rejection. This is not accurate as there is no direct nexus between the addition of the ribosomal proteins and enhancement of recombination. For example, the amended claims merely state that "at least one ribosomal protein that enhances recombinational cloning" is added to the reaction mixture. The amended claims do not explicitly link the presence of the ribosomal proteins in the claimed reaction mixture to enhanced recombinational cloning. Thus, for example, it remains indefinite as to how recombinational

cloning is enhanced for claims 31-36, 40-51, 73-76, 83-84 and 87-88. With regard to the remaining grounds of rejection made over the prior art (i.e. the Nash and Abremski et al references), the examiner can continue to make the inherency argument concerning what the prior art teaches because there is no requirement that the prior art teach that the ribosomal proteins were present in an amount sufficient to enhance the observed rates of recombination. Applicants' own specification teaches that the ribosomal proteins that are necessarily present in the crude extracts taught by the prior art would act to enhance recombination under at least some reaction conditions (i.e. those taught in the instant specification). The examiner is merely maintaining the position that the recited ribosomal proteins were present, not that they were necessarily present in quantities sufficient to enhance recombination.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the examiner has provided a rational for why one would combine the teachings of the Nash and Abremski et al references with the teachings of Hartley et al that is not dependent upon some piece of knowledge that is not readily available to the skilled artisan. Indeed, the rational is exemplified by Nash and the Abremski et al references, if not actually stated in the references. It is not necessary, or even necessarily desirable, to provide purified quantities of recombination proteins in order to obtain efficient recombination between nucleic

acids to obtain a desired product. It is, and would have been, self-evident to the skilled artisan that one can use crude extracts more quickly and with far less effort than providing homogeneous preparations of the recombination proteins to obtain the desired results, and with a reasonable expectation of success. Applicants' response has provided no rational or evidence that there would not have been a reasonable expectation of success in combining the cited teachings.

The examiner has at not point asserted that it would have been "obvious to try" the cited combinations of different teachings in the prior art. The examiner framed each of the obviousness rejections in the context of reasoned obviousness and motivation statements. Again, applicants have provided no rational or evidence as to why there would not have been a reasonable expectation of success in combining the teachings of the Nash or Abremski et al references with those of Hartley et al.

Applicants' point with regard to there being no such thing as "inherent obviousness" is understood and would be applicable to the instant rejections if the motivation provided by the examiner for combining the teachings of the cited references had anything to do with the property that the examiner has stated as being inherent to the teachings of the secondary references (i.e. Nash and the Abremski et al references). This is not the case here because the examiner is not stating that the motivation for combining the cited references has anything to do with the ribosomal proteins that are necessarily present in the crude extracts taught by the secondary references. Thus, the examiner has made no "inherent obviousness" argument in making the rejections over the prior art.

Electronic Information Disclosure Statement

Receipt is acknowledged of an electronic information disclosure statement (e-IDS) filed 1/22/2004. The signed and initialed PTO Form 1449 (Electronic Version v18) has been mailed along with this action. It is noted that in the transmittal papers for the e-IDS it is asserted that a non-electronic IDS was also filed on the same date and that only one fee should be charged to applicants. Applicants are correct that only a single fee is applicable in such an instance where the e-IDS and paper IDS are filed together. However, no paper IDS has been matched with the file to date. If one is matched to the file in the interim between this action and applicants' response, the references cited therein will be considered and PTO Form 1449 sent to applicants.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-36, 40-51, 73-76, 83-84 and 87-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is maintained for reasons of record in the office action mailed 8/11/2003 as Paper No. 28.**

Each of the claims is vague and indefinite in that the preamble of the claim recites a method for "enhancement of recombinational cloning" without a positive action step in the claim that refers back to the limitation of "enhancement". This makes it unclear as to the metes and bounds of "enhancing" recombinational cloning. Is it the addition of the recombinase or the ribosomal protein, or both, that is responsible for the "enhancement"? Or is some unrecited step

required in order to achieve "enhancement"? In what way is the reaction "enhanced"? Does this refer in some way to improving the rate of cloning or the quality of the recombination products? It would be remedial to amend the claims to clearly indicate that the enhancement refers to the stimulation of recombinational cloning due to the addition of the ribosomal proteins.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 36, 38-51, 65-72, 74-76, 87-89, 91-95, 98 and 100-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Nash (Methods in Enzymology. Vol. 100, pp210-216, see the entire reference). **This rejection is maintained for reasons of (Paper Nos. 8, 13, 25 & 28) and repeated below.**

Nash teaches the purification of the lambda Integrase (Int) protein and characterization of its activity throughout the purification process (e.g. Abstract; Table on page 214). The assay utilized to measure Integrase activity featured a linearized DNA bearing one Int recognition sequence and a supercoiled plasmid bearing a second Int recognition sequence (e.g. page 211, second paragraph-page 212, second paragraph). Recombination of the two DNA molecules produced a linear DNA having the "desirable" properties of being larger and possessing Int recognition sites attL and attR. Since Int was purified from E. coli cells after overexpression of Int from a plasmid bearing the int gene, it is inherent that the crude extracts used for the *in vitro*

assay would include the E. coli ribosomal proteins, integration host factor (IHF), HU and the Int recombinase. Nash teaches the addition of crude preparations of IHF to *in vitro* recombination mixtures to enhance recombination (e.g. page 215, second full paragraph).

It is noted that Nash teaches the "isolation" of ribosomal and recombinase proteins to varying degrees for use in the recombination reaction mixtures throughout the reference. Nash also teaches the recombinant expression of the recombinase Int (e.g. pages 212-213, *Purification*). The newly added claim limitations regarding addition of BSA, spermidine, etc., to the reaction mixture can be found in the Materials and Methods section of Nash.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-51, 65-76, 81-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al in view of Nash (U) or Abremski et al (V) or Abremski et al(W). **This rejection is maintained for reasons of (Paper Nos. 8, 13, 25 & 28) and repeated below.**

Hartley et al teach recombinational cloning methods which can be practiced *in vitro* and *in vivo* and which encompass each of the limitations of the instant claims (e.g. types of recombinases, DNA molecules used as substrates, Insert Donors, Vector Donors, etc.) (e.g. the Abstract; Figure 1; see the entire document).

Hartley et al do not teach the use of crude lysates comprising recombination factors in their *in vitro* methods. Hartley et al don't explicitly teach the addition of ribosomal proteins to their recombination reaction mixtures.

Nash teaches the purification of the lambda Integrase (Int) protein and characterization of its activity throughout the purification process (e.g. Abstract; Table on page 214). The assay utilized to measure Integrase activity featured a linearized DNA bearing one Int recognition sequence and a supercoiled plasmid bearing a second Int recognition sequence (e.g. page 211, second paragraph-page 212, second paragraph). Recombination of the two DNA molecules produced a linear DNA having the "desirable" properties of being larger and possessing Int recognition sites attL and attR. Since Int was purified from E. coli cells after overexpression of Int from a plasmid bearing the int gene, it is inherent that the crude extracts used for the *in vitro* assay would include the E. coli ribosomal proteins, integration host factor (IHF), HU and the Int recombinase. Nash teaches the addition of crude preparations of IHF to *in vitro* recombination mixtures to enhance recombination (e.g. page 215, second full paragraph). It is noted that Nash teaches the "isolation" of ribosomal and recombinase proteins to varying degrees for use in the

recombination reaction mixtures throughout the reference. Nash also teaches the recombinant expression of the recombinase Int (e.g. pages 212-213, *Purification*). The newly added claim limitations regarding addition of BSA, spermidine, etc., to the reaction mixture can be found in the Materials and Methods section of Nash.

Abremski et al (Journal of Biological Chemistry, 1984, Vol. 259, No. 3, pages 1509-1514; see the entire reference) and Abremski et al (Journal of Biological Chemistry, 1982, Vol. 257, No. 16, pages 9658-9662; see the entire document) teach the purification and characterization of the site-specific recombination enzymes Cre and Xis, respectively. Both references utilize a single recombinant vector comprising two recombination sites in an *in vitro* assay in which the products of recombination are two smaller, circular DNAs that can be cut with a single restriction enzyme and run on an agarose gel to assay formation of the different recombination products. In both instances, the enzymes were prepared from crude extracts of E. coli cells in which the enzymes were overexpressed and the enzymatic activity followed throughout the purification process (e.g. Table I of each paper). It is reasonable to expect that the E. coli ribosomal proteins as well as the E. coli proteins IHF and HU would have been present in each of the crude extracts tested.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use crude E. coli lysates comprising one or more of the recombination proteins in the methods taught by Hartley et al for recombinational cloning because 1) Hartley et al teach that their methods can be practiced *in vitro*, and because 2) Nash and the Abremski et al references teach that one can supply recombination proteins with crude extracts of E. coli cells comprising one or more recombination proteins for *in vitro* recombination reactions that

effectively produce different recombination products. One would have been motivated to do so in order to receive the expected benefit of providing one or more recombination proteins without the need for further purification and, in the case of Int/Xis, providing multiple factors known to enhance recombination. Such extracts would be expected to also comprise the ribosomal proteins expressed in E. coli. Based on the entirety of the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a crude extract comprising one or more recombination proteins to practice the recombinational cloning methods taught by Hartley et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-51, 65-76, 81-104 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of U.S. Patent No. 5,888,732 in view of Nash (U) or Abremski et al (V) or Abremski et al(W). Although the conflicting claims are not identical, they are not patentably distinct from each other for the

reasons given below. **This rejection is maintained for reasons of record in the office action mailed 8/11/2003 as Paper No. 28.**

The instant claims are drawn to *in vitro* methods of recombinational cloning wherein ribosomal proteins are also included in the recombination mixture. The cited claims from the '732 patent are all directed to *in vitro* methods of recombinational cloning which, in view of the state of the art, would encompass the use of crude cellular extracts from E. coli to provide one or more recombination proteins to the *in vitro* recombination mixture. Such crude cell extracts would be expected to comprise one or more of the E. coli ribosomal proteins.

The teachings of Nash and the Abremski et al references are described above and are applied as before.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use crude E. coli lysates comprising one or more of the recombination proteins in the methods recited in the claims of Hartley et al for recombinational cloning because the recited claims encompass *in vitro* methods wherein crude extracts are used to provide the recombination proteins, and because the Nash and the Abremski et al references teach that one can supply recombination proteins with crude extracts of E. coli cells comprising one or more recombination proteins for *in vitro* recombination reactions that produce different recombination products. One would have been motivated to do so in order to receive the expected benefit of providing one or more recombination proteins without the need for further purification and, in the case of Int/Xis, providing multiple factors known to enhance recombination. Such extracts would be expected to also comprise the ribosomal proteins expressed in E. coli based upon the extract preparation steps taught by each of the secondary references. Based on the entirety of the combined

teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a crude extract comprising one or more recombination proteins to practice the recombinational cloning methods recited by the Hartley et al claims.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
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